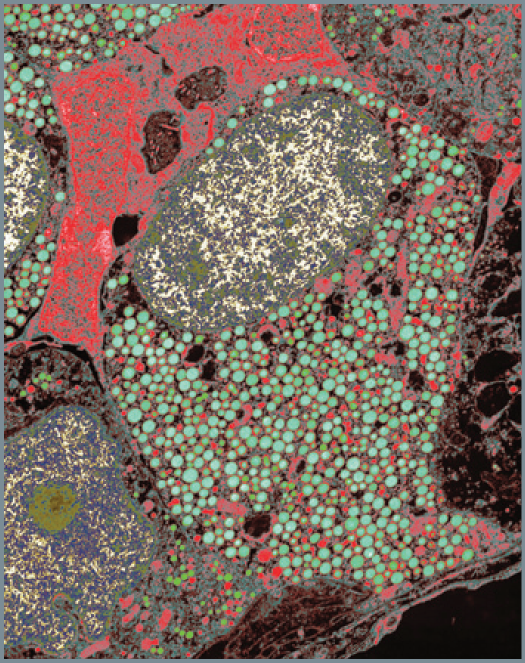

Research highlighted in this chapter describes a novel function for protein aggregates thought to be mainly associated with disease. Type 2 diabetes, like neurodegenerative diseases such as Alzheimer's disease, is associated with the appearance of amyloid protein in a patient's damaged tissues—the islet cells of the pancreas in diabetes (and the brain in Alzheimer's disease). Amyloids are defined by their structure—highly organized protein aggregates—rather than by the specific proteins that form them. Scientists supported by the NIDDK have discovered that amyloids can also have a normal biological function. In a recent study, they found that hormones can be stored as amyloids in an organized and concentrated form. This image illustrates the storage of hormones in granules (green) in a cell from the pituitary gland.

Image credit: University of Edinburgh/Wellcome Images.

Diabetes, Endocrinology, and Metabolic Diseases

NIDDK support of basic and clinical research in the areas of diabetes, endocrinology, and metabolic diseases spans a vast and diverse range of diseases and conditions, including diabetes, osteoporosis, cystic fibrosis, and obesity. Together, these diseases and conditions affect many millions of Americans and can profoundly decrease their quality of life. Many of them are complex—an interplay between genetic and environmental factors contributes to disease development.

Diabetes is a debilitating disease that affects an estimated 23.6 million people in the U.S.—or 7.8 percent of the total population—and is the seventh leading cause of death.[1] Diabetes lowers average life expectancy by up to 15 years,[2] increases cardiovascular disease risk two-to four-fold, and is the leading cause of kidney failure, lower limb amputations, and adult onset blindness.[1] In addition to these human costs, the estimated total financial cost for diabetes in the U.S. in 2007—including costs of medical care, disability, and premature death—was $174 billion.[1] Effective therapy can prevent or delay diabetic complications, but approximately one-quarter of Americans with diabetes are undiagnosed and therefore not receiving therapy.[1]

Diabetes is characterized by the body's inability to produce and/or respond appropriately to insulin, a hormone that is necessary for the body to absorb and use glucose (sugar) as a cellular fuel. These defects result in persistent elevation of blood glucose levels and other metabolic abnormalities, which in turn lead to the development of disease complications. The most common forms of diabetes are type 1 diabetes, in which the body loses its ability to produce insulin; and type 2 diabetes, in which the body becomes resistant to insulin signaling, with subsequent impaired insulin production.

Type 1 diabetes affects approximately 5 to 10 percent of individuals with diagnosed diabetes.[1] It most often develops during childhood, but may appear at any age. Type 1 diabetes is an autoimmune disease, in which the immune system launches a misguided attack and destroys the insulin-producing beta cells of the pancreas. If left untreated, type 1 diabetes results in death from starvation: without insulin, glucose is not transported from the bloodstream into the body's cells, where it is needed. Thus, patients require lifelong insulin administration—in the form of multiple daily injections or via an insulin pump—in order to regulate their blood glucose levels. Despite vigilance in disease management, with frequent finger sticks to test blood glucose levels and the administration of insulin, it is still impossible for patients to control blood glucose levels to near the normal levels achieved by functional beta cells. Thus, researchers are actively seeking new methods to improve blood glucose monitoring and insulin delivery, as well as working to develop beta cell replacement therapies to cure type 1 diabetes.

Type 2 diabetes is the most common form of the disease, accounting for about 90 to 95 percent of diabetes cases in the U.S.[1] Type 2 diabetes is associated with several factors, including older age and a family history of the disease. It is also strongly associated with obesity; more than 80 percent of adults with diabetes are overweight or obese.[3] Type 2 diabetes occurs at elevated rates among minority groups, including African Americans, Hispanic Americans, American Indians, and Native Hawaiians.[1]

In patients with type 2 diabetes, cells in muscle, fat, and liver tissue do not properly respond to insulin. As a result, blood glucose levels rise, and at first

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[1] *The National Diabetes Fact Sheet. www.cdc.gov/diabetes/pubs/factsheet07.htm*

[2] *Portuese E and Orchard T: Mortality in Insulin-Dependent Diabetes. In* Diabetes in America *(pp. 221-232). Bethesda, MD: National Diabetes Data Group, NIH, 1995.*

[3] *Eberhardt MS, et al: MMWR 53: 1066-1068, 2004.*

the pancreas produces more insulin to compensate. Gradually, however, the pancreatic beta cells lose their capacity to secrete insulin, and the timing of insulin secretion becomes abnormal. Treatment approaches for controlling glucose levels include diet, exercise, and oral and injected medications, with insulin often required as the disease progresses. There are also an estimated 57 million adults in the U.S. who have a condition called "pre-diabetes," in which blood glucose levels are higher than normal, but not as high as in diabetes.[4] This population is at high risk of developing diabetes. Fortunately, the NIDDK-supported Diabetes Prevention Program (DPP) clinical trial has shown that patients with pre-diabetes can dramatically reduce their risk of developing full-blown diabetes with diet and exercise changes designed to achieve a 7 percent reduction in body weight.

Type 2 diabetes was previously called "adult-onset" diabetes because it is predominantly diagnosed in older individuals. However, this form of diabetes is increasingly being diagnosed in children and adolescents, and it disproportionately affects minority youth. Believed to be related to increasing rates of pediatric obesity, this is an alarming trend for many reasons. First, the onset and severity of disease complications correlate with the duration of diabetes; thus, those with early disease onset are at greater risk with respect to complications than those who develop the disease later in life. Second, maternal diabetes during pregnancy—either onset of type 2 diabetes before pregnancy or the development of gestational diabetes during pregnancy—confers an increased risk of diabetes in offspring. Thus, the rising rates of diabetes and pre-diabetes in young women could lead to a vicious cycle of ever-growing rates of diabetes. Third, diabetes often becomes more difficult to control over time. With longer duration of disease, patients may find it increasingly difficult to strictly control their blood glucose levels and thus prevent or delay the development of complications. Therefore, the advent of type 2 diabetes in youth has the potential to worsen the enormous health burden that diabetes already places on the U.S. New research described in this chapter helps define the scope of the pediatric and maternal diabetes problem, and underscores the need to address this health challenge.

The NIDDK is supporting research to better understand metabolism, and the mechanisms that lead to the development and progression of diabetes and the many other endocrine and metabolic diseases within the Institute's mission; such research will ultimately spur the design of potential new intervention strategies. In parallel, based on knowledge from past scientific research investments, the Institute is vigorously pursuing studies of prevention and treatment approaches for these diseases.

GENETICS OF DIABETES

Unraveling the Genetic Causes of Type 1 Diabetes: Several recent studies are contributing to understanding the genetic underpinnings of type 1 diabetes. Scientists in the NIDDK-supported Type 1 Diabetes Genetics Consortium (T1DGC) studied over 2,400 families and discovered that variants in the *UBASH3A* genetic region were associated with the disease. They also confirmed previously reported associations with three other genetic regions (*INS*, *IFIH1*, and *KIAA0305*). A study by a different group of scientists analyzed several patient populations to follow up on results of recent genome-wide association studies (GWAS). These populations included people enrolled in the T1DGC, as well as participants from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study (DCCT/EDIC), which is a long-term NIDDK-supported study of people with type 1 diabetes. These researchers also identified *UBASH3A* as being associated with type 1 diabetes and, in addition, discovered an association in the *BACH2* genetic region. The UBASH3A protein is predominantly found in immune system cells called T cells, and *BACH2* is thought to be a regulator of the immune system's antibody response. Because type 1 diabetes is an autoimmune disease, it is plausible that defects in these genes could contribute to type 1 diabetes, although more research will help determine how these genes may play a role. In another study, scientists examined a different patient population to confirm the association between variants in the *IFIH1* genetic region and type 1 diabetes. The *IFIH1* gene was found to be more strongly expressed (turned on) in some immune system cells from people carrying variants of the gene associated with type 1 diabetes. This observation suggests that higher amounts of the protein encoded

[4] *http://diabetes.niddk.nih.gov/dm/pubs/statistics/index.htm*

by the *IFIH1* gene may be linked to increased risk for type 1 diabetes, but additional studies in more people are necessary to confirm the finding. *IFIH1* is also thought to play a role in the immune system and has been linked to two other autoimmune diseases. In another study, T1DGC scientists combined data from a new GWAS with data from previous studies to discover that over 40 different genetic regions influence a person's risk of developing type 1 diabetes. That number includes the genetic regions described above, as well as several novel regions.

Scientists are also building on recent genetics findings to understand how other genetic factors contribute to risk for type 1 diabetes. Researchers looked at previously identified type 1 diabetes susceptibility genes to determine their impact on an early stage in type 1 diabetes onset—the development of autoimmunity—in children participating in the NIDDK-supported Diabetes Autoimmunity Study in the Young (DAISY). These children were originally enrolled in DAISY because they carry variants for a different diabetes susceptibility gene (*HLA*) that put them at high genetic risk for developing type 1 diabetes. The scientists discovered that a variant in the *PTPN22* gene region increased the risk of developing autoimmunity in children with a family history of the disease. In contrast, a variant of the *CTLA-4* gene region increased the risk of autoimmunity in children without such a family history.

These studies are shedding new light on genetic factors that underlie type 1 diabetes, and may lead to enhanced ways to predict who is at high-risk for the disease, and potentially inform new intervention approaches. They also demonstrate how new knowledge is stemming from long-term, NIDDK-supported research studies based on new and emerging genetics technologies.

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Liu S, Wang H, Jin Y, Podolsky R, Reddy MV, Pedersen J, Bode B, Reed J, Steed D, Anderson S, Yang P, Muir A, Steed L, Hopkins D, Huang Y, Purohit S, Wang CY, Steck AK, Montemari A, Eisenbarth G, Rewers M, and She JX: IFIH1 *polymorphisms are significantly associated with type 1 diabetes and* IFIH1 *gene expression in peripheral blood mononuclear cells.* Hum Mol Genet *18: 358-365, 2009.*

Steck AK, Zhang W, Bugawan TL, Barriga KJ, Blair A, Erlich HA, Eisenbarth GS, Norris JM, and Rewers MJ: Do non-HLA genes influence development of persistent islet autoimmunity and type 1 diabetes in children with high-risk HLA-DR,DQ *genotypes?* Diabetes *58: 1028-1033, 2009.*

Little Genetic Overlap Between Type 1 and Type 2 Diabetes: Research has shown that there is little genetic association between the two major forms of diabetes. Because of increasing recognition that some people have clinical features of both type 1 and type 2 diabetes, scientists sought to determine whether the two diseases had common genetic underpinnings by examining whether 12 recently-identified type 2 diabetes gene regions were also involved in type 1 diabetes. (A previous study had shown that a set of genes affecting risk for type 1 diabetes does not affect the risk of type 2 diabetes.) The new study found a possible association with only one gene, called *PPARG*, which is known to play a role in type 2 diabetes. The PPARG protein is thought to have a role in the immune system, which might help explain its possible involvement in type 1 diabetes, an autoimmune disease. The overall lack of genetic overlap between the two major forms of diabetes reinforces the notion that type 1 and type 2 diabetes result from distinct physiological processes.

Raj SM, Howson JM, Walker NM, Cooper JD, Smyth DJ, Field SF, Stevens HE, and Todd JA: No association of multiple type 2 diabetes loci with type 1 diabetes. Diabetologia 52: 2109-2116, 2009.

PANCREATIC PROGENITOR CELLS

New Insights into Pancreatic Development: New studies are providing key insights into the progenitor cells that give rise to different cell types in the pancreas. Both type 1 and type 2 diabetes are characterized by loss of functional beta cells, the pancreatic cells that produce the hormone insulin. Strategies to repopulate beta cells, either by transplant or by induction of new beta cell formation, show promise in treating diabetes. Toward successful therapeutic strategies, scientists are making progress in identifying, characterizing, and understanding the factors and mechanisms that underlie pancreatic development. In addition to the insulin-producing beta cells, the pancreas is composed of multiple other cell types. Some of these—like beta cells—produce hormones released into the blood to regulate the body's metabolism; these cell types are termed "endocrine." Other cell types produce proteins that aid in the digestion of food; these cell types are termed "exocrine." In order to promote the formation of new beta cells, scientists, including members of the NIDDK-supported Beta Cell Biology Consortium, are determining when and how certain pancreatic progenitor cells become "committed" to developing into specific endocrine or exocrine cell types.

In one study, scientists investigated the role of a group of proteins, called presenilins, in specifying pancreatic cell types in mice. They studied cells that have Ngn3, a well-established marker of embryonic pancreatic progenitor cells, and discovered that the activity of presenilins was needed to block the cells from becoming exocrine cells. This showed that Ngn3 was not sufficient to commit pancreatic progenitor cells to endocrine cell types. Rather, cells that have Ngn3 can become endocrine or exocrine cells—a flexibility of Ngn3 cells that was previously unknown. In a second study, using elegant labeling techniques to mark a single mouse pancreatic progenitor cell and monitor its progression, another group of scientists focused on the Ngn3 cells that become endocrine cells and found that these cells are "unipotent" precursors. That is, Ngn3 is a marker shared in common by cells destined to develop into different endocrine cell types, but each individual Ngn3-containing cell is committed to becoming only one of the endocrine cell types. In fact, unlike other progenitor cells that proliferate to generate many mature cells, Ngn3-containing cells often appeared not to proliferate at all, with each one simply morphing into its final endocrine cell type. These findings are important because understanding the characteristics of progenitor cells that can turn into beta cells can help inform new strategies toward generating new beta cells to replace those impaired by diabetes.

In a final study, scientists uncovered additional plasticity in a pancreatic endocrine cell type—the alpha cell. Using genetic techniques in mice, the researchers increased the levels of a protein called Pax4, which is known to be involved in promoting cells to develop into endocrine cell types. They found that mice with high levels of Pax4 had oversized clusters of beta cells, which resulted from alpha-beta precursor cells and established alpha cells being induced to form beta cells. In addition, in a mouse model of diabetes, the high levels of Pax4 promoted generation of new beta cells and overcame the diabetic state. The discovery that alpha cells have the potential to convert to beta cells, and the additional insights into pancreatic progenitor cells made in the other studies, generate a fuller picture of pancreatic development. These advances may pave the way toward new cell-based therapies for diabetes.

Collombat P, Xu X, Ravassard P, Sosa-Pineda B, Dussaud S, Billestrup N, Madsen OD, Serup P, Heimberg H, and Mansouri A: The ectopic expression of Pax4 *in the mouse pancreas converts progenitor cells into alpha and subsequently beta cells. Cell 138: 449-462, 2009.*

Cras-Méneur C, Li L, Kopan R, and Permutt MA: Presenilins, Notch dose control the fate of pancreatic endocrine progenitors during a narrow developmental window. Genes Dev 23: 2088-2101, 2009.

Desgraz R and Herrera PL: Pancreatic neurogenin 3-expressing cells are unipotent islet precursors. Development 136: 3567-3574, 2009.

AUTOIMMUNITY IN TYPE 1 DIABETES

***Deaf1* Gene May Play a Role in Type 1 Diabetes:** Scientists identified a gene that may play a role in the development of type 1 diabetes. Examining genes from a mouse model of type 1 diabetes, the scientists found that cells in the animals' pancreatic lymph nodes make two forms of the same gene called deformed epidermal autoregulatory factor 1 (*Deaf1*). One form of this gene encodes full-length, functional Deaf1 protein, while the other encodes a shorter, nonfunctional variant form. The research suggests that the full-length, functional form of Deaf1 may control the production of molecules needed to eliminate immune cells that can destroy insulin-producing cells in the pancreas, causing type 1 diabetes. Moreover, the presence of the Deaf1 variant was found to prevent the full-length Deaf1 protein from functioning normally. Additional experiments showed that the variant form inhibited turning on genes needed to produce certain molecules involved in immune regulation. Researchers also found that levels of the variant form of Deaf1 were higher in people with type 1 diabetes compared to levels in people without the disease. In addition, the human variant form inhibited the full-length form from functioning normally. The research suggests that the development of type 1 diabetes may in part be due to increased levels of the Deaf1 variant protein in pancreatic lymph nodes. Increased levels of Deaf1 variant may, in turn, lead to reduced production of molecules that are required to educate the immune system not to attack the body's own cells, including the insulin-producing cells of the pancreas. Furthermore, the findings suggest that the Deaf1 variant form may predict risk for type 1 diabetes and be a target for therapy.

Yip L, Su L, Sheng D, Chang P, Atkinson M, Czesak M, Albert PR, Collier AR, Turley SJ, Fathman CG, and Creusot RJ: Deaf1 isoforms control the expression of genes encoding peripheral tissue antigens in the pancreatic lymph nodes during type 1 diabetes. Nat Immunol 10: 1026-1033, 2009.

B Lymphocytes Do the Shuffle: "Receptor Editing" as a Marker for Type 1 Diabetes: Scientists discovered that patients with autoimmune diseases have lower levels of "receptor editing" in the B lymphocytes of their immune systems than healthy individuals—a discovery that may lead to changes in strategies for treatment of some patients with type 1 diabetes. In mammals, B cells generate diverse antibodies to recognize a variety of potential foreign invaders, such as viruses or bacteria. The DNA that encodes an antibody undergoes rearrangements to create antibodies that can recognize different substances. Sometimes an errant B cell produces an antibody that recognizes "self"—the body's own cells. As one way to correct the error, the DNA in the B cell can be shuffled again, a process called "receptor editing."

In patients with autoimmune diseases, however, the process of receptor editing seems to falter. In this study, scientists designed a new assay to investigate the timing and incidence of editing during B cell development by measuring the occurrence of rearrangement with a non-functional segment of antibody DNA. Other assays of autoimmunity rely on measurements of the antibodies themselves once a B cell has matured (a late event). This new assay allows measurement of earlier events potentially associated with autoimmunity, as editing occurs during B cell development in the bone marrow while the cell is still maturing. Understanding the timing of this process could provide insight about whether or how to direct B cell-targeted therapies. To investigate the level of receptor editing in autoimmune diseases, the scientists first conducted their assay with mouse models of type 1 diabetes and systemic lupus erythematosus. Mice that had already developed autoimmunity showed a reduced level of editing, indicating that reduced editing is associated with autoimmune disease. In addition, in further experiments the scientists observed that mice prone to autoimmunity showed lower levels of editing even before autoimmune disease developed; this result suggests that reduced editing could indicate a predisposition towards the development of autoimmunity rather than arising as a consequence.

To determine whether this association was also found in people, the researchers examined B cells from adult patients with type 1 diabetes or systemic lupus erythematosus. They found that some of the patients had low levels of receptor editing when compared to healthy individuals. This indicates that the low levels may be correlated with these diseases, but that not all autoimmunity results from reduced receptor editing. Critically, these results suggest that current therapies to temporarily delete mature B cells may not be effective in patients with reduced receptor editing, because new B cells that recognize "self" will continue to be generated in the bone marrow, unimpeded by editing. This new assay to measure receptor editing could facilitate personalized treatments for patients with type 1 diabetes or lupus by helping to determine who may benefit from B cell therapies. Technical features of the assay additionally make it potentially applicable to other autoimmune diseases. Further research will show whether the assay may also provide an early indication of increased risk for developing autoimmunity.

Panigrahi AK, Goodman NG, Eisenberg RA, Rickels MR, Naji A, and Luning Prak ET: RS rearrangement frequency as a marker of receptor editing in lupus and type 1 diabetes. J Exp Med *205: 2985-2994, 2008.*

NIDDK Director Testifies on *Special Diabetes Program*

On June 24, 2009, NIDDK Director Dr. Griffin P. Rodgers testified about progress in type 1 diabetes research before the Senate Committee on Homeland Security and Governmental Affairs. The hearing, entitled "Type 1 Diabetes Research: Real Progress and Real Hope for a Cure," was chaired by Senators Joe Lieberman and Susan Collins. Dr. Rodgers spoke of research made possible by the *Special Statutory Funding Program for Type 1 Diabetes Research*, including the discovery of at least 40 genetic regions linked to type 1 diabetes, and progress from clinical trials testing approaches to delay or prevent the disease. A hearing on type 1 diabetes research is held every 2 years in conjunction with the Juvenile Diabetes Research Foundation (JDRF) Children's Congress. The previous day, Dr. Rodgers received the JDRF Children's Congress Heroes Award for his work in advancing type 1 diabetes research and improving the lives of people affected by the disease.

At the June 2009 congressional hearing on type 1 diabetes, JDRF Children's Congress delegates (foreground) listened to testimony from (at table, left to right) JDRF International Chair Mary Tyler Moore, NIDDK Director Dr. Griffin Rodgers, boxing legend Sugar Ray Leonard, and singer/songwriter Nick Jonas. Several of the children and a parent also spoke at the hearing, describing their experiences with this disease and the importance of research.

RISK FACTORS FOR DIABETES IN YOUTH

Height Growth Rate Is Associated with Type 1 Diabetes Development in At-Risk Children: Researchers discovered an association between progression to type 1 diabetes in children and an accelerated rate of height growth (change in height over time). Type 1 diabetes results from a complex interplay of both genetic and environmental causes. Since 1993, the Diabetes Autoimmunity Study in the Young (DAISY) has followed children at increased type 1 diabetes genetic risk for the development of autoimmunity—a pre-clinical phase that often precedes the clinical diagnosis—and type 1 diabetes. Following these high-risk children for many years allows the scientists to note changes as the children age and to monitor who develops the disease and who does not.

In one recent analysis of data collected from the DAISY study, the scientists compared height, weight, body mass index (BMI, a measure of weight relative to height)—and the rates of change of these characteristics—between children who developed autoimmunity and type 1 diabetes and children who did not. They found that, in children ages 2 to 11 and genetically prone to the disease, a greater rate of height growth was associated with the development of autoimmunity and strongly associated with progression to type 1 diabetes in children with autoimmunity. They did not observe a strong correlation between autoimmunity or type 1 diabetes development and final height, weight, BMI, or growth rate of weight or BMI. Previous studies suggested an association between increasing BMI, weight, and height and incidence of type 1 diabetes in the general population, but this study was specific to genetically at-risk children ages 2 to 11. Understanding how more rapid height change could trigger autoimmunity and type 1 diabetes may help to elucidate how the disease develops. For example, rapid growth might stress the insulin-producing beta cell. Additional research could confirm and determine the reason for the association between increased height growth rate and type 1 diabetes development.

Lamb MM, Yin X, Zerbe GO, Klingensmith GJ, Dabelea D, Fingerlin TE, Rewers M, and Norris JM: Height growth velocity, islet autoimmunity and type 1 diabetes development: the Diabetes Autoimmunity Study in the Young. Diabetologia *52: 2064-2071, 2009.*

Studies Highlight Health Disparity in Risk Factors for Type 2 Diabetes in Middle School Children: Researchers have found a high level of risk for future diabetes and cardiovascular disease among middle school students. Scientists recruiting sixth-grade students for a new intervention study found that minority students were at greater risk for type 2 diabetes than Caucasians. HEALTHY is a 3-year intervention study designed to test approaches for reducing risk factors for type 2 diabetes in middle school children. The intervention involves making changes to the school environment: improving nutrition, increasing the students' physical activity, and helping the students and their families make behavior changes. Prior to the start of the intervention, the researchers collected blood samples and other information from the students to examine the prevalence of type 2 diabetes risk factors for this population of children. Over 6,000 sixth-grade students attending 42 schools in the U.S. were included in the survey. At every school, at least half of the students were eligible for free or reduced-priced lunch or belonged to a minority group. Investigators measured three different characteristics in students—body mass index (BMI, a measure of weight relative to height), fasting blood glucose levels, and fasting insulin levels—to determine if they had risk factors for type 2 diabetes. A high BMI and elevated fasting blood glucose and insulin levels have been linked to development of type 2 diabetes. The researchers recently reported their findings.

Overall, nearly half of the sixth-grade students in schools participating in the HEALTHY study were considered overweight or obese according to their BMI. This is higher than the national average of U.S. children, but similar to rates observed in other predominantly minority populations. Among the students in the study, the Hispanic children had the greatest percentage of overweight/obese individuals, followed by African American children. In addition to measuring BMI, investigators also determined the fasting blood glucose and fasting insulin levels of the students. Sixteen percent of the students had relatively high levels of blood glucose while fasting (pre-diabetes), and almost 7 percent had elevated fasting insulin levels. Similar to the findings on BMI, the highest percentage of pre-diabetes and elevated fasting insulin levels was observed in Hispanic students. Together, these results indicate the importance of research focusing on children, particularly those in populations similar to those in the HEALTHY study, to test interventions to reduce the risk of type 2 diabetes with the hope of achieving long-lasting improvements to children's health.

Another study examined a racially and ethnically diverse group of eighth-grade students participating in a pilot study for HEALTHY to see what fraction met the International Diabetes Federation (IDF) metabolic syndrome definition. The "metabolic syndrome" refers to a group of risk factors that increase the likelihood of developing cardiovascular disease and type 2 diabetes. Standard definitions of the metabolic syndrome apply only to adults.

Recently, the IDF developed a definition for children. According to IDF criteria, an adolescent has metabolic syndrome if he or she has a large waist circumference ($\geq$90th percentile) and two or more of the following: high blood triglycerides (a type of fat that increases risk for heart disease); low HDL ("good cholesterol"); high blood pressure; or elevated fasting blood glucose.

The researchers found that, overall, 9.5 percent of the children in the HEALTHY pilot study met the IDF pediatric definition for metabolic syndrome—double the rate previously found among American teens in the general population. More than 80 percent of the children included in the analysis were Hispanic or African American—groups at an increased risk of type 2 diabetes. Moreover, 50 percent of the children were overweight. This result, along with the results from HEALTHY, highlights a disparity in disease risk among adolescent Hispanic and African American children and underscores the importance of diabetes and cardiovascular disease prevention efforts to address health disparities among children.

Kaufman FR, Hirst K, Linder B, Baranowski T, Cooper DM, Foster GD, Goldberg L, Harrell JS, Marcus MD, and Treviño RP, for the HEALTHY Study Group: Risk factors for type 2 diabetes in a sixth-grade multiracial cohort: the HEALTHY study. Diabetes Care *32: 953-955, 2009.*

Jago R, Baranowski T, Buse J, Edelstein S, Galassetti P, Harrell J, Kaufman F, Linder B, and Pham T, for the Studies to Treat or Prevent Pediatric Type 2 Diabetes Prevention Study Group: Prevalence of the metabolic syndrome among a racially/ethnically diverse group of U.S. eighth-grade adolescents and associations with fasting insulin and homeostasis model

assessment of insulin resistance levels. *Diabetes Care* *31: 2020-2025, 2008.*

Maternal Diabetes Accelerates Type 2 Diabetes Diagnosis in Offspring: A surveillance study of diabetes in youth has found that children with type 2 diabetes received their diagnosis at an earlier age if their mothers had been diagnosed with diabetes prior to pregnancy—adding to the body of evidence about the long-term effects of intrauterine exposure to diabetes on offspring. These results come from the SEARCH for Diabetes in Youth Study. SEARCH is a large, population-based study of diabetes in racially and ethnically diverse youth.

To learn more about why higher rates of type 2 diabetes in children are associated with maternal diabetes, SEARCH investigators compared the parental diabetes history of over 2,600 youth diagnosed with either type 1 or type 2 diabetes before age 20. They found that not only were youth with type 2 diabetes nearly eight times more likely than those with type 1 diabetes to have a mother with diabetes, but they were also more likely to have been diagnosed more than 18 months sooner, on average, if their mothers already had diabetes while pregnant than if they didn't. These findings held for all ethnic and racial groups studied. The results of this study build on earlier studies of diabetes in youth among the Pima Indians of Arizona, by showing that the increased risk of diabetes conferred by intrauterine exposure to diabetes is not restricted to this population. Moreover, SEARCH found that, among the children with type 2 diabetes whose mothers also had diabetes, girls had an earlier age of diagnosis than boys by over a year on average. These findings are especially troubling in light of the cycle in which earlier onset of type 2 diabetes leads to greater likelihood of maternal type 2 diabetes and in turn increased risk in offspring, and lend urgency to efforts to break this cycle and thus reduce one of the risk factors for diabetes in youth.

Pettitt DJ, Lawrence JM, Beyer J, Hillier TA, Liese AD, Mayer-Davis B, Loots B, Imperatore G, Liu L, Dolan LM, Linder B, and Dabelea D: Association between maternal diabetes in utero and age at offspring's diagnosis of type 2 diabetes. *Diabetes Care* *31: 2126-2130, 2008.*

Prevalence of Overweight and Obesity in Young Americans with Diabetes: In recent decades, overweight and obesity rates in children have risen dramatically in the U.S., with a disproportionate impact on minority youth. Obesity puts young people at risk of developing other conditions, such as diabetes. While the relationship between obesity and type 2 diabetes is well known, less is understood about how overweight or obesity affects type 1 diabetes development.

To improve understanding of the degree to which increased body fat contributes to the risk of diabetes among American youth with either form of diabetes, researchers determined the prevalence of overweight and obesity in young Americans with type 1 or type 2 diabetes, compared to those without diabetes. To do so, they utilized data collected from 2001 to 2004 as part of a large, multi-center, population-based study with diverse racial and ethnic representation, called the SEARCH for Diabetes in Youth study (SEARCH). Results of this study were compared with information collected during the same timeframe on young Americans without diabetes who participated in the National Health and Nutrition Examination Survey (NHANES), led by the Centers for Disease Control and Prevention (CDC). Scientists analyzed and compared data collected from Americans younger than 20 years old in both these studies to assess the contribution of overweight or obesity, based on the body mass index (a measure of weight relative to height), to a medical diagnosis of type 1 or type 2 diabetes. As anticipated, a majority (79.4 percent) of the children and adolescents with type 2 diabetes were obese and an additional 10.4 percent were overweight. Overall, young people with type 1 diabetes were more likely to be overweight (22 percent vs. 16 percent), but not obese, compared to youth who did not have diabetes. Researchers could not determine whether the increase in overweight preceded the diagnosis of type 1 diabetes or was caused by its therapy. Intensive therapy with insulin to control glucose levels and reduce diabetes complications is associated with an increased risk of overweight.

As the largest racially and ethnically diverse study to date focused on the prevalence of overweight and obesity in American children and adolescents with diabetes, this study provides information that is critical to understanding and addressing this issue. By showing an association between excess weight and type 1 diabetes, as well as supporting earlier findings of the link between obesity and type 2 diabetes, this new study highlights areas for future investigation, aimed at improving care for these chronic conditions in young people in the U.S.

Liu LL, Lawrence JM, Davis C, Liese AD, Pettitt DJ, Pihoker C, Dabelea D, Hamman R, Waitzfelder B, and Kahn HS for the SEARCH for Diabetes in Youth Study Group: Prevalence of overweight and obesity in youth with diabetes in USA: the SEARCH for Diabetes in Youth Study. Pediatr Diabetes 2009 May 15. [Epub ahead of print]

DIABETES AND HEART DISEASE

Treating Heart Disease in People Who Have Diabetes: New results from a randomized clinical trial in nearly 2,400 patients indicate that optimal medical therapy is as beneficial as elective revascularization procedures in patients with type 2 diabetes and stable coronary heart disease. Type 2 diabetes more than doubles the risk of heart attack and stroke and also worsens outcomes after these events. While revascularization (*e.g.*, coronary bypass surgery or angioplasty) has proven beneficial in treating severe forms of coronary artery disease, its benefits for people with diabetes and stable coronary artery disease have been uncertain.

Led by the National Heart, Lung, and Blood Institute with support from NIDDK, the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) multi-center, international clinical trial simultaneously compared two cardiovascular treatment approaches—revascularization procedures and optimal medical therapy—and two diabetes control strategies, in an effort to identify ways to improve patient survival and to lower the risk of heart attacks and strokes. Optimal medical therapy includes intensive drug therapy and lifestyle interventions, such as dietary changes and smoking cessation. After an average patient follow-up of 5 years, BARI 2D found no overall difference between revascularization procedures and medical therapy in lowering the risk of death, heart attack, and stroke. The researchers did see an intriguing difference among patients within the revascularization group. Although the study was not designed to compare the efficacy of different forms of revascularization in patients for whom this is an elective procedure, researchers observed that patients who had prompt bypass surgery, rather than angioplasty, as their form of revascularization, had significantly fewer non-fatal heart attacks or strokes compared to similar patients who initially received optimal medical therapy alone. However, participants who were treated with bypass surgery, and their counterparts in the medical therapy group, were also more likely to have had more extensive coronary artery disease when they entered the trial than those who were treated with angioplasty—possibly explaining the relative difference in outcome with the two revascularization procedures. More research is needed to confirm the findings about bypass surgery in type 2 diabetes patients for whom this is an elective procedure. Researchers also found no difference between the two diabetes control strategies tested in the trial. Because heart disease is the leading cause of death in people with diabetes, findings such as these are important to help inform treatment choices by patients and health care providers.

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Understanding Heart Health in Youth with Type 1 Diabetes: New research by the SEARCH for Diabetes in Youth study showed that youth with type 1 diabetes and suboptimal control of their blood glucose levels had abnormal lipid (fat) profiles, even after a short duration of disease. Diabetes is a major risk factor for heart disease, but most studies on the link between the two diseases have been done in adults. To determine if lipid abnormalities appear at young ages, SEARCH investigators compared lipid profiles in youth with and without type 1 diabetes, and examined if variations in lipid profiles were associated with differences in blood glucose control. Lipid profiles, such as measurements of total cholesterol and LDL ("bad") cholesterol, are related to risk of heart disease in adults. The youth in the study were 10 to 22 years old and had had type 1 diabetes for an average of about 4 years. The scientists found that youth with type 1 diabetes and optimal blood glucose control (HbA1c less than 7.5 percent) had similar lipid levels as non-diabetic youth. However, youth with type 1 diabetes and suboptimal glucose control (HbA1c of 7.5 percent or greater) had elevated lipid levels, including high total and LDL cholesterol. Regardless of blood glucose control, youth with the disease had elevated apolipoprotein B levels and had more small, dense LDL particles (two types of lipids associated with heart disease risk in adults) compared to non-diabetic youth. These results suggest that youth with type 1 diabetes have abnormal lipid levels, even after a relatively short duration of disease. However, good blood glucose control may help protect against these abnormalities, which provides further impetus for people with type 1 diabetes to implement early and intensive blood glucose control.

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REGULATORS OF METABOLISM IN HEALTH AND DISEASE

Insulin, Metformin, and Pathways of Glucose Production in Fasting and Obesity: New research is shedding light on the ways metabolism in the liver is affected by obesity and by two of the most widely prescribed medications for people with diabetes. Insulin, produced naturally by the body in response to elevated glucose in the blood, is prescribed to all patients with type 1 diabetes because they cannot make the vital hormone themselves. It is also prescribed to many people with type 2 diabetes in cases where other medications cannot make up for lost insulin production capacity and their bodies' increased needs for the hormone. The most widely prescribed medication for type 2 diabetes, however, is metformin, which works by reducing the amount of glucose fed into the bloodstream by the liver. A hormone called glucagon triggers the liver to release glucose during periods of fasting. For reasons that have not been fully understood, liver glucose production occurs even in the absence of fasting in people with diabetes, contributing to elevated blood glucose. One of insulin's key effects is to blunt the impact of glucagon, stopping its release of liver glucose, and accounting for one of its most serious side effects. Overly high doses of insulin not only send glucose levels too low, they also limit the ability of glucagon to bring glucose back up again. The result is hypoglycemia, dangerously low blood glucose. Metformin also counteracts glucagon, but rarely causes hypoglycemia by itself, because it does not directly lower blood glucose by signaling cells to take up glucose as insulin does.

New research in obese mice fed a high-fat diet clarifies the pathway that leads to excessive production of glucose from the liver in type 2 diabetes, and pinpoints the ways in which metformin and insulin interrupt the process. One group of researchers found that a complex of proteins acts to boost glucose output and is triggered both by fasting signals (glucagon) and by a cellular condition that can result from obesity, called the "ER (endoplasmic reticulum) stress response" (see Cross-Cutting Science chapter). Another group of researchers found that both insulin and metformin lead to a modification of one of the proteins in this complex—a protein called CBP. The modification of CBP causes the complex to fall apart so that it no longer supports glucose production. Although the impact on CBP and glucose production is the same, metformin and insulin work through different pathways to modify CBP, which helps explain why metformin is effective even in patients who are resistant to insulin's effects. Understanding the molecular pathways by which the healthy liver promotes glucose control, as well as how insulin and metformin work in disease, has the potential to help improve glucose control in diabetes patients, preventing both hypoglycemia and the long-term complications of hyperglycemia (high blood glucose). Because metformin is currently the only approved drug in its class, this research may also help to identify new and better therapeutic strategies to help people with diabetes control their blood glucose.

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Wang Y, Vera L, Fischer WH, and Montminy M: The CREB coactivator CRTC2 links hepatic ER stress and fasting gluconeogenesis. Nature 460: 534-537, 2009.

A Metabolic Sensor Controls Energy Balance, Inflammation, and Insulin Resistance: Scientists have discovered how a key regulatory protein controls metabolic function and "energy balance"—the balance between energy (in the form of calories) ingested and energy burning or storage. The proper balance of energy intake, storage, and usage is a fundamental aspect of human health, as the disruption of the energy balance equation often leads to metabolic disorders such as type 2 diabetes, metabolic syndrome, and obesity. Regulation of the body's energy balance involves an extensive and intricate network of cellular metabolic pathways. At the center of this network is a protein called SIRT1. Acting as a "metabolic sensor," SIRT1 directs cells to turn on or off different pathways that either use or store energy in response to the energy needs of the cell. In two new studies, scientists have uncovered how SIRT1 coordinates with different pathways in different tissues to influence metabolic function.

In the first study, researchers found that SIRT1 coordinates with another key regulator of cellular energetics, the AMP-activated protein kinase (AMPK). AMPK senses and responds to levels of energy deprivation, such as during fasting or starvation, and directs cells to start breaking down stores of fat. To do this, AMPK activates a protein known as PGC-1alpha, which subsequently turns on the genes involved in fat metabolism. By studying this process in mice and in laboratory-grown mouse cells, scientists discovered that PGC-1alpha activation requires not just AMPK, but the coordinated effort of AMPK and SIRT1. When cells were treated to reduce their levels of SIRT1, AMPK could not activate PGC-1alpha, and genes involved in fat metabolism were not turned on. Previous studies have shown that SIRT1 can turn on PGC-1alpha by removing specific chemical modifications that normally inhibit its function. The researchers in this study found that this "modifying" function of SIRT1 was activated indirectly by AMPK, where AMPK raises the amount of a small cellular signaling molecule that is required for SIRT1 function. Although AMPK and SIRT1 have both previously been implicated in PGC-1alpha activation, this study provided the first evidence that they act together in a coordinated fashion to regulate energy expenditure.

In the second study, researchers discovered that SIRT1 also plays a key role in glucose (sugar) metabolism by regulating the response to insulin in adipose (fat) tissue. When they compared mice with diet-induced obesity to "normal" mice, the researchers observed that the levels of SIRT1 in adipose tissue were dramatically decreased in the obese mice. Using laboratory-grown adipose cells, the scientists then showed that a decrease in SIRT1 protein levels correlated with impaired insulin signaling and the decreased ability of adipose cells to take up glucose. In addition to promoting insulin resistance, SIRT1 deficiency also appears to result in a state of chronic inflammation: The scientists found that SIRT1 protein acts in an anti-inflammatory fashion by removing chemical modifications from, and thereby inactivating, NF-kappaB, a key protein that turns on an inflammatory response. When the researchers suppressed the inflammatory response, either by reducing NF-kappaB protein levels or by using pharmacologic agents that activate SIRT1 (and, thus, inactivate NF-kappaB), they found that adipose cells have improved insulin signaling and improved insulin-stimulated glucose uptake. These results put SIRT1 in the center of a pathway connecting insulin resistance and inflammation. Based on their anti-inflammatory effect, activators of SIRT1 may turn out to be a useful therapeutic intervention for improving insulin sensitivity as a means of treating type 2 diabetes.

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Yoshizaki T, Milne JC, Imamura T, Schenk S, Sonoda N, Babendure JL, Lu JC, Smith JJ, Jirousek MR, and Olefsky JM: SIRT1 exerts anti-inflammatory effects and improves insulin sensitivity in adipocytes. Mol Cell Biol 29: 1363-1374, 2009.

The Right To Assemble—Aggregates of Hormones in Health and Disease: Scientists discovered a normal biological function for a type of protein aggregate generally associated with disease. Type 2 diabetes, like Alzheimer's disease and some other neurodegenerative diseases, is associated with the appearance of "amyloids" in a patient's damaged tissues—the pancreatic islet cells in diabetes and the brain in Alzheimer's disease. Amyloids are defined by their structure—characteristic filamentous aggregates—rather than by the specific proteins that form them. It is unknown whether amyloids are a cause or a consequence of the diseases associated with them.

In this study, the scientists found that certain hormones can be stored as amyloids in a highly organized and concentrated form. When the scientists exposed these hormone amyloids to conditions similar to those that exist during hormone secretion, they disassembled, releasing the hormones as would be required if the amyloids serve as storage depots in advance of secretion. Interestingly, the scientists showed that the effects can be toxic if the amyloid packages are opened at the wrong time or place. They hypothesized that conditions like diet, stress, or age could alter the physiological balance that regulates the release of hormone amyloids and lead the amyloids to collect and aggregate, as seen in disease. In the pancreas, this build-up of amyloids might induce the insulin-producing beta cells of the pancreas to die, leading to the dramatic loss of beta cells seen in type 2 diabetes. Additional research is necessary to test these hypotheses and to better understand the role of amyloids in health and disease, but this exciting result provides an important insight in basic hormone biology.

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Neuro-Protective Peptide May Also Regulate Insulin Sensitivity: A small protein that can protect brain cells from death in Alzheimer's disease may also open up new avenues to improving insulin action in people with type 2 diabetes. The protein, called humanin, promotes brain cell survival in the face of Alzheimer's disease and other forms of brain injury. Because there is increasing evidence for an association between insulin resistance and Alzheimer's disease, scientists hypothesized that humanin might also positively affect insulin sensitivity.

Using a technique called insulin clamping, which allows scientists to observe changes in insulin sensitivity under different experimental conditions (such as normal or high levels of insulin), the researchers tested whether humanin could affect insulin sensitivity in rodent models. They found that rats that were treated with humanin in the hypothalamus—a part of the brain that helps govern the rest of the body's response to insulin—showed increased insulin sensitivity over rats that received a control treatment. This positive effect was seen even in rats that had experimentally induced high levels of insulin (hyperinsulinemia), which in humans is a symptom of insulin resistance. In the hyperinsulinemic rats, infusing humanin into the brain increased insulin sensitivity in both major target tissues of insulin action, liver and muscle. When delivered intravenously instead of into the brain, "normal" humanin did not increase insulin sensitivity in the rats, but a specially modified, more potent form of the protein did—demonstrating that humanin's effect on insulin sensitivity may be achieved without direct administration into the brain. In diabetic rats, a single intravenous injection of the more potent form of humanin was able to reduce the animals' blood glucose levels for several hours.

Insulin resistance is a feature of many diseases and disorders, including type 2 diabetes, pre-diabetes, obesity, and cardiovascular disease. This study adds to the evidence for its association with Alzheimer's disease and other brain diseases as well. While these experiments were conducted in rodents, and more remains to be learned about the role of humanin in regulating insulin action, the study findings may point toward new approaches to treating type 2 diabetes.

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Protein Factor Allows Fructose To Fuel Metabolic Diseases: New research has identified a molecular connection between consumption of the dietary sugar, fructose, and metabolic problems, including type 2 diabetes. Increased consumption of fructose, commonly used as a sweetener in sodas and processed foods, has roughly paralleled the dramatic increases in overweight and obesity observed since the 1970s. Although it is thought that a complex interplay of many factors has driven the obesity epidemic in the U.S., the widespread use of fructose has been proposed as a potential contributing factor. Fructose consumption has been linked to metabolic abnormalities such as nonalcoholic fatty liver disease and type 2 diabetes. Further, fructose has been shown to be a more potent trigger of fat production in the body than other sugars, although the reasons for this have been unclear.

New research has implicated the protein PGC-1beta as playing a key role in mediating the metabolic effects of fructose. When rats are fed a diet rich in fructose, they develop symptoms associated with the metabolic syndrome and type 2 diabetes in humans, including weight gain, an unhealthy blood lipid profile, and high blood glucose and insulin levels. Researchers experimentally diminished PGC-1beta in rats fed a high-fructose diet, and found that this protected the rats from fructose-induced weight gain, as well as other metabolic abnormalities linked to fructose, such as insulin resistance and excessive production of glucose by the liver. Diminishing PGC-1beta conferred a more modest benefit in rats with insulin resistance due to a high-fat diet. In contrast, reducing the amount of PGC-1beta in rats fed a standard diet actually increased their liver glucose production. These results suggest that PGC-1beta promotes the metabolic problems associated with a high-fructose diet. The data also support the idea that reducing consumption of fructose may help some people avoid overweight, obesity, and some of the diseases associated with them, and suggest that a therapeutic approach targeting PGC-1beta may be beneficial for some people with metabolic syndrome or type 2 diabetes.

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Keeping an Even Energy Keel from Meal to Meal: Research in mice is providing new insights into the way the mammals regulate their energy supply. The body needs energy at all times to keep cells and organs functioning. But the supply of energy from food is not constant. Eating typically provides more fuel than is necessary at precisely that moment, so the excess must be appropriately stored. In contrast, periods of fasting and starvation require liberation of a sufficient supply of stored energy to keep the organism going until the next meal—which may be hours, days, or weeks away. New discoveries are identifying the molecular triggers that control mammalian responses to a varying energy supply.

One study showed that insulin, the hormone that instructs cells to take up glucose following feeding, triggers a protein called DNA-PK to modify another protein called USF-1, which then activates genes involved in storing energy as fat. This is surprising, because DNA-PK was known for playing a key role in repairing genetic damage, but had not previously been understood to play a part in metabolism.

When a mammal is eating regularly, a ready energy supply in the liver keeps its body going between meals. When the length of time between feedings is extended long enough to deplete that ready supply, however, the body enters starvation mode and must avail itself of other energy depots. A second study identified molecular factors in this fasting-to-starvation transition. Researchers found that a hormone called FGF21 induces the liver to make the protein PGC-1 alpha, which then turns on genes controlling processes like the burning of fat for fuel and the production of glucose from other energy stores.

These results improve understanding of metabolic regulation in healthy mammals—regulation that may go awry in disease. Such fundamental knowledge may also lead to improved treatment for metabolic diseases, including diabetes and obesity.

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To Understand Bone Formation, Just Follow Your Gut: Scientists made a surprising discovery that bone formation is regulated by levels of gut-derived serotonin, and a gene called *Lrp5* controls bone formation by inhibiting serotonin production. Bone is living tissue that constantly rebuilds as old bone tissue is broken down and new bone is formed. The *Lrp5* gene had previously been found to be important in bone formation. Mice lacking *Lrp5* have low bone mass due to a decrease in bone formation. In people, mutations in this gene are associated with bone diseases, including a form of osteoporosis. However, it was unknown how *Lrp5* regulated bone formation, whether it was acting directly on the bone, and what other cellular factors were involved.

To understand how *Lrp5* regulates bone formation, scientists first sought to identify factors controlled by *Lrp5* by determining whether any genes were turned on or off differently in bones of mice lacking *Lrp5* as compared to normal mice. In mice lacking *Lrp5*, they found that the gene turned on to the greatest extent is involved in serotonin synthesis, and the activity of this gene was also increased dramatically in gut cells. The animals also had abnormally high levels of serotonin. Only about 5 percent of the body's serotonin is produced in the brain, where it modulates mood, appetite, sleep, and other processes. The other 95 percent is made in the duodenum of the gastrointestinal tract, but the function of this gut-derived serotonin has been a matter of scientific debate.

With these clues about the importance of gut-derived serotonin, the scientists performed a series of experiments in mice to examine serotonin's role in bone formation. In one experiment, they found that administration of a chemical inhibitor of serotonin synthesis normalized bone formation in mice lacking *Lrp5*. In another experiment, they discovered that genetically turning off serotonin production in the gut protected against bone loss in a mouse model of menopause (a time period when women are at greater risk for loss of bone density). Overall, the research showed that increasing serotonin levels slowed the formation of new bone, while inhibiting serotonin production promoted it. In addition, the research demonstrated that Lrp5 was not acting directly on bone, but rather in the gut to regulate production of serotonin, which in turn travels through the body to inhibit bone formation. Studies in a small number of people with bone diseases associated with mutations in *LRP5* showed that the patients have abnormal serotonin levels. These preliminary observations suggest that serotonin may also be important in controlling bone formation in people. Most drugs for osteoporosis that are approved for use in people prevent the breakdown of bone, but do not promote the generation of new bone. The discovery that gut-derived serotonin inhibits bone formation in mice and possibly in people suggests that therapies to inhibit serotonin production in the gut, or to block its action on bone, could be a novel means by which to treat or preempt osteoporosis.

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CIRCADIAN RHYTHM AND METABOLISM

Circadian Rhythm and Metabolism Depend on Changes in Gene Activity Caused by Histone Modifications: A newly uncovered link between circadian rhythm and metabolism may yield therapeutic targets for metabolic diseases. In animals and humans, the circadian clock regulates many behaviors and bodily processes—including sleep/wake cycles, changes in blood pressure, and body temperature fluctuations—to harmonize these activities with daily, rhythmic changes in the environment, most notably day/night cycles. The circadian clock also has a critical relationship with metabolic pathways important to maintaining normal energy balance. Identifying the molecular signals that link circadian rhythm and metabolism could yield important insights into metabolic disorders and diseases such as insulin resistance, diabetes, and obesity and how to thwart their development. Scientists now have evidence that interactions between circadian clock genes and metabolic genes are governed by transitory changes to the proteins associated with DNA, called "histones," and have identified two key factors in these interactions. By chemically modifying histones, the cell is able to physically "open up" or "close down" access to underlying DNA and thereby dynamically regulate gene expression (whether genes are turned "on" or "off").

In a new study in mouse models, researchers used genetic techniques to disrupt the interaction between a histone-modifying protein and a partner protein that both recruit the histone-modifying protein to circadian genes and activate it. They found that the mutant mice had abnormal patterns of circadian gene expression, and their circadian behaviors were disrupted. More significantly, the mutant mice grew to be leaner than their normal littermates, more sensitive to insulin, and resistant to obesity from a high-fat diet. Molecular studies revealed that the cyclic expression of several metabolic genes had been significantly altered in the mutant mice, reinforcing that the timing of expression of metabolic genes is critical for normal energy balance. Although these studies were carried out in mice, the results suggest that altering circadian rhythm by inducing a different pattern of histone-modification at circadian clock genes can potentially have positive metabolic effects. Future studies may exploit these findings to more precisely define the changes that yield metabolic benefit and develop new approaches to help prevent metabolic diseases.

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The Rhythm of Metabolism: Scientists have identified a genetic link between fasting glucose levels and melatonin, a molecule that regulates circadian rhythms. The circadian rhythm is a roughly 24-hour cycle that humans and other organisms use to anticipate changes in their external environment, such as light and dark, and thus establish sleeping and feeding cycles. Previous studies uncovered a relationship between circadian rhythms and the body's metabolism, leading scientists to hypothesize that metabolic disorders, including obesity and type 2 diabetes, might be linked to disruption of circadian rhythms.

Elevation of blood glucose levels is associated with diabetes, but even among people who do not have diabetes there is variation in fasting blood glucose levels. Researchers recently performed a genome-wide association study to scan a set of common genetic variations throughout the genome for those associated with high or low fasting glucose levels. Identification of such variations could help scientists understand how glucose levels are regulated in the body and how these levels can become unregulated in disease. Genetic data from several previous studies were combined, so that this study effectively included over 36,000 individual genomes from people of European descent. The researchers found that a variant in a gene called *melatonin receptor 1B* (*MTNR1B*) was consistently associated with elevated fasting glucose levels. In addition, this variant was associated with reduced pancreatic beta cell function. Beta cells, which synthesize and secrete insulin, are critical for normal control of glucose levels. Moreover, the variant was associated with an increased risk of development of type 2 diabetes.

The product of the *MTNR1B* gene is known to interact with melatonin. Melatonin levels are lowest during the day and peak at night, whereas insulin levels drop at night. This suggests that insulin levels may be controlled, at least in part, by an inhibitory effect of melatonin on insulin secretion. Thus, the identification of *MTNR1B* as a factor in fasting blood glucose levels helps explain the relationship between glucose regulation and circadian rhythms, and provides evidence in humans for a link between melatonin and type 2 diabetes. Interestingly, fasting blood glucose is typically measured in the morning, so that study participants do not have to miss daytime meals. This may have helped the researchers to identify the circadian link. By shedding light on the biology of glucose metabolism, this study may eventually help lead to a new therapeutic avenue to treat people with type 2 diabetes.

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HE, Willemsen G, Witteman JC, Yuan X, Zhao JH, Zeggini E, Schlessinger D, Sandhu M, Boomsma DI, Uda M, Spector TD, Penninx BW, Altshuler D, Vollenweider P, Jarvelin MR, Lakatta E, Waeber G, Fox CS, Peltonen L, Groop LC, Mooser V, Cupples LA, Thorsteinsdottir U, Boehnke M, Barroso I, Van Duijn C, Dupuis J, Watanabe RM, Stefansson K, McCarthy MI, Wareham NJ, Meigs JB, and Abecasis GR: Variants in MTNR1B *influence fasting glucose levels. Nat Genet 41: 77-81, 2009.*

NEW SCREENING TEST FOR INBORN ERRORS OF METABOLISM

Improved Test Offers Hope for Children Born with Mucopolysaccharidosis I: A new diagnostic test may help doctors identify babies born with the lysosomal storage disorder mucopolysaccharidosis I (MPS I) early enough to provide optimal therapy. The body's cells recycle many of the substances they no longer need by digesting them with enzymes inside cellular compartments called lysosomes. If these enzymes are missing or defective due to genetic mutations, toxic waste products are not properly degraded. Instead, they build up in the lysosomes and lead to severe organ damage. Diseases caused by these enzyme deficiencies are referred to collectively as lysosomal storage disorders. Symptoms vary, and are often not apparent at birth. However, as the undigested materials accumulate, they can cause serious problems such as weakness, severe pain, brittle bones, mental retardation, corneal clouding, organ failure, and death. In recent years, scientists discovered that many of these symptoms can be alleviated by administering the missing enzyme directly to affected patients. However, in order for this type of therapy to confer maximal benefit, it is important to start treatment early on in a patient's life. The new test can allow clinicians to diagnose the disorder before symptoms develop by analyzing a spot of dried blood for the activity of the enzyme missing in MPS I. The researchers who developed the test had sought to improve on a previous diagnostic assay they had developed, and note that features of the new test make it easier and more practical to use. If further evaluation confirms the utility of this new test for newborn screening, it may enable enzyme replacement therapy or bone marrow transplant to take place early enough to avert many of the most serious symptoms of the disease.

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CYSTIC FIBROSIS RESEARCH

Genetic Risk Factor Identified for Liver Disease Development in Cystic Fibrosis: An international scientific collaboration has resulted in the discovery of the first genetic risk factor for severe liver disease development in some people with cystic fibrosis (CF). CF is an inherited disease that affects mainly the lungs, pancreas, and sweat glands. However, many individuals with CF also develop abnormal liver function and fibrosis, with some progressing to severe liver disease. The major genetic defects responsible for CF are mutations in the gene called *CFTR*, which result in mucus accumulation in airways and abnormal function of other organs. However, the process by which liver disease develops in individuals with CF is unclear, and patients with the mutated *CFTR* gene exhibit a wide range of disease severity. Based on these observations, additional genetic factors likely play a role in determining susceptibility to liver disease development in patients with CF. Currently, no diagnostic test exists to identify which individuals with CF are at high risk of developing severe liver disease.

Researchers, at sites around the globe, worked together to identify genetic risk factors associated with severe liver disease development in CF. They increased their chances of finding these genetic factors by performing two sequential studies of patients with CF and healthy controls: an initial study examining five genes suspected of contributing to CF liver disease, followed by a second study to confirm these genetic associations. In the initial study, two genetic variants, one in the *SERPINA1* gene, referred to as the *SERPINA1 Z* allele, and another in the *TGFB1* gene, were associated with CF liver disease; however, the second study confirmed only *SERPINA1 Z* allele as a risk factor. When the data from both studies were combined for greater statistical power, the *SERPINA1 Z* allele was shown to have a strong association with CF liver disease. The *SERPINA1 Z* allele is known to cause proteins to fold incorrectly and accumulate in liver cells; however the mechanism by which it contributes to CF liver disease requires further study.

This research identifies the *SERPINA1 Z* allele as the first genetic factor that increases the risk of developing severe liver disease in individuals with CF. This discovery allows for the possibility of future infant screening programs that follow up on diagnosis of CF by testing for their genetic susceptibility to develop severe liver disease later in life, so that appropriate preemptive action can be taken.

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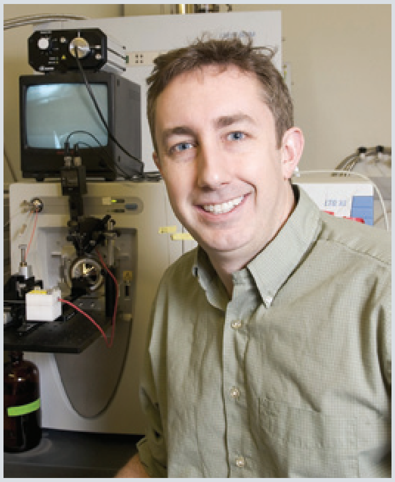
Improved Treatment for Diabetes Related to Cystic Fibrosis: A new study has revealed that a diabetes treatment can benefit many patients with an increasingly common complication of cystic fibrosis. CF, a genetic disorder that leads to chronic lung infections, once led inevitably to childhood death from scarring of the lungs. New treatments are helping people with CF live much longer—often into their 30s and 40s. However, as they age, an increasing number of people with CF are developing CF-related diabetes (CFRD), which has been associated with reduced survival. CF severely damages the pancreas, affecting first its vital role in producing digestive enzymes needed for food absorption from the intestine, and later its production of insulin needed to transport glucose fuel into cells. Replacement of lost digestive enzymes improves growth and nutrition, but sufficient insulin is also needed to maintain body weight and muscle mass. Still, because patients with CFRD may not be at risk for many of the serious complications associated with other forms of diabetes, the benefit of adding insulin therapy to the already burdensome CF treatment regimen has been uncertain. A recent clinical trial has now shown that aggressive insulin therapy, begun earlier in the course of their diabetes than previously recommended, can help many people with CFRD maintain their body weight and potentially avoid the excess mortality associated with CFRD.

Moran A, Pekow P, Grover P, Zorn M, Slovis B, Pilewski J, Tullis E, Liou TG, Allen H, and the Cystic Fibrosis Related Diabetes Therapy Study Group: Insulin therapy to improve BMI in cystic fibrosis-related diabetes without fasting hyperglycemia: results of the cystic fibrosis related diabetes therapy trial. Diabetes Care *32: 1783-1788, 2009.*

Dr. Michael J. MacCoss and Dr. Kristin V. Tarbell: NIDDK-Supported Scientists Receive Presidential Award

Two scientists supported by NIDDK have received the Presidential Early Career Award for Scientists and Engineers (PECASE). PECASE is awarded annually to scientists and engineers who, while early in their research careers, have demonstrated the pursuit of innovative research and outstanding scientific leadership. Among the recipients in 2007 was Michael J. MacCoss, Ph.D., an NIDDK extramural grantee, and in 2008, Kristin V. Tarbell, Ph.D., a scientist in NIDDK's Division of Intramural Research. In addition to the NIDDK-supported recipients, in both years, 11 other scientists supported by the NIH received the award for their scientific achievements; NIH has now funded 153 PECASE recipients since the award's inception in 1996. PECASE is the most prestigious award given in the U.S. to scientists at the outset of their independent research careers.

Developing Cutting-Edge Technologies To Study Health and Disease



Dr. Michael J. MacCoss

Dr. MacCoss, an Assistant Professor in the Department of Genome Sciences at the University of Washington in Seattle, received a 2007 PECASE award for his innovative work in the emerging field of "proteomics"—the large-scale, "big-picture" view of all of the proteins that make up a cell. Of interest to Dr. MacCoss, however, is not so much what proteins are in a cell, but rather the dynamics of how quickly proteins are made and how quickly they are destroyed. The balance of making and destroying proteins is an essential way to control how much time a protein can spend carrying out its specific cellular function, an important aspect of normal health and disease. To facilitate the study of "quantitative proteomics," as it is known, Dr. MacCoss' research group is developing innovative technologies that will allow scientists to map out the dynamic life cycle, or turnover, of proteins within a cell. His team is applying these tools to model organisms to study how insulin—a hormone that regulates uptake of glucose by a cell—affects the turnover of proteins involved in cellular metabolism. As insulin and a cell's ability to respond to insulin are intimately linked to type 2 diabetes, Dr. MacCoss' studies may provide new fundamental insight into how protein turnover regulates the cellular response to insulin and alters the response in type 2 diabetes.

Understanding Immune Tolerance and Type 1 Diabetes

Dr. Kristin V. Tarbell

Dr. Tarbell, a tenure-track investigator in the Diabetes Branch of NIDDK's Division of Intramural Research, received a 2008 PECASE for her seminal research studying immune tolerance and autoimmunity. The human immune system protects the body from foreign, potentially harmful molecules and organisms. Since the body does not want to attack itself, the immune system has a set of suppressive features, known as immune tolerance, that prevent its inappropriate activation. When these mechanisms are compromised, however, the aberrant attack of "self" often results in autoimmune diseases such as type 1 diabetes. While a Research Associate at Rockefeller University, where she received an NIDDK Mentored Research Scientist Development Award, Dr. Tarbell made important discoveries regarding how two types of immune cells—dendritic cells (DCs) and regulatory T cells (Tregs)—interact to suppress the autoimmune response that causes type 1 diabetes. Importantly, Dr. Tarbell and her colleagues showed that Tregs, when activated by DCs, can be used to block the development of diabetes or reverse diabetes in mice. Since joining NIDDK, Dr. Tarbell and her research group have continued to explore how both DCs and Tregs can be used to suppress the autoimmune response that causes type 1 diabetes. Future advances from Dr. Tarbell's research should provide fundamental insight on how autoimmunity develops, which may translate into new therapeutic approaches for reversing type 1 diabetes in patients.

The PECASE awards support the continued professional development of awardees, promote careers and foster innovation in science and technology, and recognize the scientific missions of participating agencies. A list of NIH scientists who have received this prestigious award is available at *www.grants.nih.gov/grants/policy/pecase.htm*

Diabetes Mellitus Interagency Coordinating Committee: Coordinating the Federal Investment in Diabetes Programs To Improve the Health of Americans

Diabetes places huge personal and economic burdens on Americans. However, even as rates of diabetes are rising, people with diabetes are living longer and healthier lives. Advances in medicine, public health, and health care have led to significant progress. New research discoveries and translation efforts will yield further improvements in the prevention, diagnosis, and treatment of diabetes. Building on the accomplishments and successes of Federal programs in improving public health with regard to diabetes, the government agencies responsible for leading the Federal investment in diabetes are working together to improve the health of Americans.

Congress created the statutory Diabetes Mellitus Interagency Coordinating Committee (DMICC) in 1974 with the charge to coordinate diabetes research activities and health programs of the National Institutes of Health and other Federal agencies, and to provide for the communication and exchange of information necessary for coordination. Chaired by the NIDDK, the DMICC has 35 members representing diverse agencies within the U.S. Department of Health and Human Services (DHHS), the U.S. Department of Defense, the U.S. Department of Agriculture, and the Veterans Health Administration. These member organizations have important, unique, and complementary roles in the Federal diabetes effort to improve public health.

Individual Federal agencies have made significant, measurable strides in combating diabetes. However, many successful efforts have required a combination of expertise and resources not found in a single organization. Interagency coordination through the DMICC is thus essential to avoid unnecessary duplication of diabetes activities, to maximize the value of available resources, and to ensure the optimal use of federal funds to combat and alleviate the public health burden of diabetes. The DMICC coordinates federal diabetes activities and works to share information, foster joint efforts, and identify opportunities for agency collaboration.

Since its inception, the DMICC has facilitated successful, collaborative diabetes activities among its member organizations. For example, the National Diabetes Education Program, the leading Federal Government public education program that promotes diabetes prevention and control, is jointly overseen by the NIDDK and Centers for Disease Control and Prevention. Another example, the landmark Diabetes Prevention Program clinical trial, which dramatically showed that type 2 diabetes can be prevented or delayed, involved many DMICC member organizations. *The National Diabetes Fact Sheet*, a product of collaborations among DMICC member organizations, summarizes the latest estimates of Americans with pre-diabetes and with diagnosed and undiagnosed diabetes, helping those at Federal, State, and local levels understand the health and economic burden of diabetes. Further highlights of major areas of successful collaboration include coordination of the trans-DHHS *Special Statutory Funding Program for Type 1 Diabetes Research* and strategic planning for diabetes research programs.

In response to the immense and growing public health burden of diabetes, the DMICC has been expanding and enhancing its efforts. The DMICC is uniquely poised to leverage Federal resources, reduce redundancy of effort, and increase public awareness of Federal diabetes research, programs, and health information to combat the diabetes epidemic.

The DMICC recently developed a booklet to increase awareness of the Committee and the many diabetes activities coordinated by its member organizations. Entitled "DMICC: Coordinating the Federal Investment in Diabetes Programs To Improve the Health of Americans," the new booklet includes information about the Committee, its member organizations, the coordination of Federal diabetes efforts, and the activities and successes of the Committee. The Committee's booklet is available in electronic form through its Web site: *www.diabetescommitee.gov* Hard copies of the publication are available through the National Diabetes Information Clearinghouse at: *http://catalog.niddk.nih.gov*

The Improved Outlook for People with Type 1 Diabetes

In the 1950s, about one in five people died within 20 years after a diagnosis of type 1 diabetes. About one in four people developed kidney failure within 25 years of diagnosis. About 90 percent of people with type 1 diabetes developed diabetic retinopathy within 25 years of diagnosis. People monitored their blood glucose levels with urine tests, which recognized high, but not dangerously low, glucose levels and reflected past, not current, glucose levels.

Today, the outlook for people with type 1 diabetes is greatly improved due to landmark studies that demonstrated the importance of early intensive blood glucose control and due to improvements in technology. The NIDDK's landmark Diabetes Control and Complications Trial (DCCT) and its follow-up study, the Epidemiology of Diabetes Intervention and Complications (EDIC), recently demonstrated that near-normal control of glucose beginning as soon as possible after diagnosis can greatly improve the long-term prognosis of type 1 diabetes. The study also found that the prognosis for people with longstanding type 1 diabetes has greatly improved in the past 20 years due to a better understanding of the importance of intensive glucose control, as well as advances in insulin formulations, insulin delivery, glucose monitoring, and the treatment of cardiovascular risk factors.

The DCCT, conducted from 1983 to 1989, compared intensive management of blood glucose to conventional control in 1,441 people 13 to 39 years of age with recently diagnosed type 1 diabetes. At the time, conventional treatment consisted of one or two insulin injections a day with daily urine or blood glucose testing. Participants randomly assigned to intensive treatment were asked to keep glucose levels as close to normal as possible. That meant trying to keep hemoglobin A1c (HbA1c) readings at 6 percent or less with at least three insulin injections a day or an insulin pump, guided by frequent self-monitoring of blood glucose. (HbA1c reflects average blood glucose levels over the previous 2 to 3 months.)

The DCCT found that intensive glucose control was superior to conventional control in delaying or preventing the complications of type 1 diabetes. EDIC continues to follow DCCT participants to determine the long-term effects of prior intensive versus conventional blood glucose control. In the most recent study, the researchers compared overall rates of eye, kidney, and cardiovascular complications in three groups of people diagnosed with type 1 diabetes an average of 30 years earlier.[1] Two groups consisted of DCCT/EDIC participants—those randomly assigned to intensive glucose control or to conventional control. The third group was a subset of patients in the NIDDK-supported Pittsburgh Epidemiology of Diabetes Complications (EDC) study. The EDC is a population-based study that has been following residents of Allegheny County, Pennsylvania, who were diagnosed with type 1 diabetes from 1950 to 1980.

After 30 years of diabetes, DCCT participants randomly assigned to intensive glucose control had about half the rate of eye damage compared to those assigned to conventional glucose control (21 percent vs. 50 percent). They also had lower rates of kidney damage (9 percent vs. 25 percent) and cardiovascular events (9 percent vs. 14 percent) compared to those receiving conventional glucose control. The intensively treated DCCT group also had lower complication rates than EDC participants, whose rates were similar to the DCCT's conventional group. These observations suggest that implementing intensive glucose control as early in the course of diabetes as possible could help people avoid the life-threatening complications that were much more common in the past.

Major improvements in glucose monitoring and insulin delivery introduced in the past decade are now helping patients control their blood glucose more precisely and conveniently and reduce the risk of hypoglycemia. For example, several continuous glucose monitoring devices approved by the U.S. Food and Drug Administration give both trend and real-time information on glucose levels. Insulin pump technology is also improving, and researchers have begun testing a system that combines both technologies in patients with newly diagnosed type 1 diabetes. With early intensive therapy to control blood glucose levels and improvements in technology, the outlook for people diagnosed with type 1 diabetes is better than ever.

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[1] *Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group, Nathan DM, Zinman B, Cleary PA, Backlund JY, Genuth S, Miller R, and Orchard TJ: Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983-2005). Arch Intern Med 169: 1307 -1316, 2009.*

Research Provides the Power To Prevent Type 2 Diabetes

In the early 1990s, public health experts recognized a developing type 2 diabetes crisis. Rising rates of obesity and an aging populace were driving worldwide prevalence of the disease higher—fast. In many parts of the world that had previously recorded low rates of diabetes, alteration of traditional lifestyles was leading to a diabetes explosion. As an extreme example, rates of type 2 diabetes in the Pima Indians of Arizona, aged 30 to 64—among whom the disease was once all but unknown—exceeded 50 percent in 1994.[1] Many racial and ethnic groups, including African Americans, Alaska Natives, American Indians, Asian Americans, Hispanics/Latinos, and Pacific Islanders, are disproportionately impacted by type 2 diabetes. Rates of type 2 diabetes are climbing in much of the world, but are particularly high in the U.S., where about 24 million people now have diabetes.

What was lacking in the early 1990s was any proven way to do something about the problem; although type 2 diabetes was linked to the obesity epidemic, no one knew whether losing weight would prevent diabetes, or how much weight needed to be lost. In addition, while there were several drugs available to treat diabetes once it developed, no one knew whether any of these could also prevent the disease. Scientists did know how to identify people at elevated risk of type 2 diabetes. Some people have "impaired glucose tolerance" (IGT)—their bodies have become somewhat resistant to the effects of insulin, so they are unable to produce enough of the hormone to keep glucose at a normal level in the blood. This condition places people at substantially higher risk of developing diabetes in the future than people whose blood glucose stays within the normal, healthy range. For this reason, IGT is sometimes called "pre-diabetes." People who have this condition and who are also overweight are a group that scientists hope to help with a diabetes prevention strategy.

The enormous costs associated with type 2 diabetes, including premature death, blindness, kidney failure, amputation, and heart disease, as well as its economic burden, are compounded by the progressive difficulty of treating type 2 diabetes with longer duration of disease. These factors have made type 2 diabetes a critical target for prevention. The dramatic rise in diabetes among the Pima and other American Indian groups strongly suggested that a change in lifestyle had precipitated the problem, and if so, a change in lifestyle might also help to alleviate it. Therefore NIDDK researchers and grantees proposed to test whether changes in diet and physical activity designed to yield modest weight loss might reduce the risk of type 2 diabetes in those at risk. That idea came to be the Diabetes Prevention Program (DPP) clinical trial.

The Diabetes Prevention Program

In the DPP, adult participants from 27 clinical centers around the U.S. were randomly divided into different treatment groups. The first group, called the lifestyle intervention group, received intensive training in diet, physical activity, and behavior modification. By eating less fat and fewer calories and doing moderate exercise, such as brisk walking, for a total of 150 minutes a week, they aimed to lose 7 percent of their body weight and maintain that loss. This intervention was based on extensive behavioral research that suggested it would be a sustainable approach to modest weight loss for a high proportion of participants. The second group took the generic diabetes drug metformin twice a day. The third, a control group, received placebo pills instead of metformin. The metformin and placebo groups also received information about diet and exercise, but no intensive behavior change counseling. A fourth group was treated with the drug troglitazone, but this part of the study was discontinued after researchers discovered that troglitazone can cause serious liver damage. The participants in this last group were followed but not included as one of the intervention groups. All 3,234 study participants were overweight or obese and had pre-diabetes. Forty-five percent of the participants belonged to racial and ethnic groups at increased risk for developing diabetes, including the Pima Indians of the Gila River Reservation in Arizona, and three additional American Indian tribes.

The study was a tremendous success. The lifestyle intervention reduced participants' risk of developing diabetes by 58 percent. Lifestyle changes worked particularly well for participants age 60 and older, reducing their risk by 71 percent, and were equally effective for all participating ethnic groups and for both men and women. Participants taking metformin lowered their risk of developing diabetes by 31 percent. Metformin was effective for both men and women, but was most effective in people 25 to 44 years old and in those with a body mass index of 35 or higher, meaning they were at least 60 pounds overweight.

Researchers announced the initial findings of the DPP in 2001, a year earlier than scheduled, because the results were so striking. In 2002, the National Diabetes Education Program (NDEP), jointly sponsored by the NIDDK and the Centers for Disease Control and Prevention, launched a comprehensive prevention initiative, *Small Steps. Big Rewards. Prevent Type 2 Diabetes*, to translate the results of the DPP Study into public health practices (*http://ndep.nih.gov/campaigns/SmallSteps/SmallSteps_index.htm*). The campaign delivers practical, real-world tools to help people take the small steps needed to achieve the big reward of preventing or delaying type 2 diabetes.

The DPP Outcomes Study

The success of the DPP notwithstanding, DPP researchers could not say how long the benefit would endure, since the results were based on just 3 years of data. Because the benefit of the DPP lifestyle intervention was indisputable, all three groups were offered a group-based lifestyle intervention. The Diabetes Prevention Program Outcomes Study (DPPOS) began, with most of the DPP volunteers taking part. Metformin treatment continued in the metformin group, and the lifestyle intervention group was offered additional lifestyle support. By following the participants for a total of 10 years after enrollment in the DPP, researchers have concluded that the lifestyle intervention reduced the rate of developing type 2 diabetes by 34 percent compared with placebo. Study participants in the lifestyle interventions group also had fewer cardiovascular risk factors, including lower blood pressure and triglyceride levels, despite taking fewer drugs to control their heart disease risk. Treatment with metformin reduced the rate of developing diabetes by 18 percent compared with placebo over the 10 year period.[2]

Building on the Results of the DPP

Today, NIDDK is supporting translational research to find better methods for identifying people with pre-diabetes and to develop cost-effective ways of implementing the DPP lifestyle change in communities. One innovative study is working with YMCAs to deliver a DPP-based lifestyle intervention. Other research efforts, such as the Action for Health in Diabetes (Look AHEAD) clinical trial, which seeks to reduce complications in those who have the disease, has built on the success of the DPP lifestyle intervention, and achieved even greater weight loss by modifying the lifestyle intervention. Through these and other efforts, the signal scientific achievements of the DPP continue to drive new health discoveries, while transforming the effort to prevent type 2 diabetes and its devastating complications.

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[1] *Prevention of diabetes mellitus: Report of a WHO study group (ISBN: 92 4 120844 9).*

[2] *Knowler WC, Fowler SE, Hamman RF, Christophi CA, Hoffman HJ, Brenneman AT, Brown-Friday JO, Goldberg R, Venditti E, and Nathan DM, for the Diabetes Prevention Program Research Group: 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet 374: 1677-1686, 2009.*

Resistin: Looking Forward and Back

Dr. Mitchell Lazar

Dr. Mitchell Lazar is the Sylvan H. Eisman Professor of Medicine and Genetics at the University of Pennsylvania School of Medicine. He is also the Chief of the University's Division of Endocrinology, Diabetes, and Metabolism, and is the Director of the Institute of Diabetes, Obesity, and Metabolism. He received his M.D. degree and a Ph.D. in Neuroscience from Stanford University's School of Medicine. Dr. Lazar's research has been supported by NIDDK since 1991, including two MERIT awards. In addition to serving on the NIDDK's Advisory Council, Dr. Lazar has been elected to the American Society of Clinical Investigation, the Association of American Physicians, the Institute of Medicine of the National Academy of Sciences, as well as the American Academy of Arts and Sciences. Dr. Lazar is the 2009 recipient of the American Society for Clinical Investigation's Stanley J. Korsmeyer Award, in recognition of his outstanding contributions to our understanding of the regulation of metabolism.

The following are highlights from the scientific presentation that Dr. Lazar gave to the NIDDK's Advisory Council in May 2009 on new understanding of the role of the hormone resistin, which was discovered in his laboratory.

The current epidemics of obesity and type 2 diabetes have occurred during a time of tremendous change in our lifestyles, particularly in regard to diet and physical activity. How these environmental changes have influenced these epidemics is an important research question. Obesity is a risk factor for the development of type 2 diabetes, but an understanding of how these two states are related at a molecular level has proved difficult to unravel. Type 2 diabetes is characterized by a change in the ability of tissues to respond to insulin, a hormone that regulates the body's use and storage of energy sources (calories from food). In this state—known as insulin resistance—insulin is less able to promote the uptake of glucose in muscle and fat, and to inhibit the production of glucose by the liver. Once tissues start to become insulin resistant, the pancreas, the organ that produces insulin, tries to compensate by secreting more insulin, but the body eventually can become even more resistant to insulin. Obesity increases risk for insulin resistance, which can lead to type 2 diabetes.

One of the keys to elucidating the relationship between obesity and insulin resistance is to understand how increased energy storage in fat cells, referred to as "adipocytes," promotes resistance to insulin in muscle and liver. In the presence of excess calories, insulin works to promote storage of the calories as fat in fat tissue and to induce transport of glucose into fat and muscle tissues. Scientists previously thought that adipose (fat) tissue was simply a storehouse, a place to put the excess. Research over the past 2 decades has revealed that adipocytes secrete hormones that affect other tissues and organs in the body. Many of these secreted proteins are involved in metabolic processes, including glucose regulation. Could they also be involved in insulin resistance? By looking at a class of type 2 diabetes drugs called thiazolidinediones that improve insulin sensitivity, scientists discovered that the insulin-sensitizing drugs worked through a protein found in adipocytes known as PPAR-gamma. Since PPAR-gamma is in fat cells, while insulin resistance occurs primarily in liver and muscle cells, the scientists thought that there must be a factor regulated by PPAR-gamma that is secreted from fat cells to affect those other tissues.

Identification of a Novel Factor Produced by Fat Cells in Mice: Resistin

PPAR-gamma receives signals from outside the cell and then induces changes in whether various genes are turned on or off ("gene expression"). Dr. Lazar hypothesized that the insulin-sensitizing drugs, through interaction with PPAR-gamma, may dampen the activity of a gene in fat cells involved in insulin resistance. Thus, to identify new adipocyte molecules that mediated insulin resistance, Dr. Lazar's laboratory looked for genes that were turned off by this class of insulin-sensitizing drugs in mice. They identified a gene that was suppressed in adipocytes by these drugs and named it "resistin" for its role in resistance to insulin. Mouse resistin is specifically produced and secreted by adipocytes. Resistin's secretion from the fat cells into the blood circulation is consistent with its potential role in affecting insulin resistance of other body tissues. In their study, Dr. Lazar and his colleagues showed that levels of resistin in the blood were increased in obese mice, including mice with a genetic mutation conferring obesity, and mice that were obese from having been fed a high-fat diet. Increasing levels of circulating resistin, by injecting resistin protein into mice, promoted insulin resistance. In contrast, decreasing levels of circulating resistin in mice, by injecting a factor that "neutralized" resistin protein, improved insulin sensitivity and decreased levels of blood glucose.

Further research in Dr. Lazar's laboratory revealed that resistin was a member of a novel family of secreted proteins in rodents and humans, and increased understanding of resistin's protein chemistry. Using genetic manipulations, Dr. Lazar and his colleagues showed that chronically high levels of resistin in mice of normal weight led to insulin resistance. By generating mice that lacked resistin (through genetic manipulations), Dr. Lazar and his colleagues found that mice without resistin were protected against insulin resistance. These genetic findings were confirmed by similar research in a number of laboratories. The results of these studies all nicely demonstrated that resistin was potentially an important regulator of insulin sensitivity and a promising candidate to link obesity to insulin resistance and diabetes.

Differences Emerge Between Mouse and Human Resistin

While research in mice provided important discoveries about the role of resistin, studies of resistin in humans were not so clear. A number of laboratories investigated whether high levels of resistin were linked to diabetes, obesity, and insulin resistance in people. Among the first published reports, many studies described a correlation between increased resistin levels and metabolic problems in humans. However, there were also studies that did not observe a correlation. More recent studies of resistin in humans that used larger population samples more convincingly link elevated levels of resistin to increased risk of type 2 diabetes. These studies also identify genetic variations associated with high resistin levels that correlate with insulin resistance in specific populations. These studies are providing further evidence that resistin, if not a causative factor, may be at least a biomarker of type 2 diabetes. Additional studies, including research from Dr. Lazar's team, show correlations between resistin levels and coronary atherosclerosis and increased risk of coronary artery disease. Other studies have shown that resistin levels are reduced by statin drugs and that very high resistin levels are correlated with a marked increase in the likelihood of heart failure.

So the studies increasingly suggest that resistin may be a factor in human metabolic diseases, including diabetes. But, not long after the discovery of resistin, another confusing issue arose: although mouse resistin is produced exclusively in white adipose tissue, several laboratories around the world (including Dr. Lazar's) found that human resistin is produced by cells of the body's immune system—known as monocytes and macrophages. This raised an interesting question:

Might the human resistin found in immune system cells have a similar metabolic function as the mouse resistin found in fat cells? Around this time, other researchers reported that adipose tissue is surprisingly not a pure population of fat cells, but contains macrophages as well, and that inflammation—a response of the immune system—is linked to metabolic conditions, like obesity and diabetes. By linking fat tissue and the immune system, these discoveries suggested that mouse and human resistin could be functioning in a similar manner despite their different cellular origins.

Human Resistin Links Inflammation and Metabolic Disease

To test whether inflammation affected levels of resistin in humans, Dr. Lazar and his colleagues injected healthy volunteers with a molecule that stimulates inflammation and a strong immune response. Researchers had previously noted that during this induced inflammatory state, people become temporarily insulin-resistant. Dr. Lazar's team measured levels of resistin following the injection and observed that resistin levels markedly increased in the stimulated inflammatory state. This and additional studies of the relationship between resistin and inflammation suggest that, in humans, inflammation is characterized by increased resistin levels.

Can macrophage-derived human resistin exacerbate metabolic disease, though? To answer this, Dr. Lazar and his colleagues turned their studies back to mice. This time they developed mice that were genetically engineered so that they would only produce the <u>human</u> version of resistin, not the native mouse resistin, and would only produce it in their macrophages, not in fat cells. The scientists compared these mice with littermates that didn't have any resistin to determine whether it is harmful to have macrophage-produced resistin.

Dr. Lazar and his laboratory found that, after 2 weeks of a high-fat diet, the mice carrying the human version of resistin were glucose intolerant and resistant to insulin—hallmarks of type 2 diabetes. Therefore, macrophage-derived human resistin contributed to insulin resistance in these mice. In addition, the expression of genes associated with inflammation was increased in the adipose tissue of these mice, indicating that resistin's ability to promote inflammation contributes to its role in insulin resistance. These results demonstrate that macrophage-produced human resistin promoted insulin resistance in mice fed high-fat diets, much like adipocyte-produced mouse resistin did in normal mice. These results also indicate that human resistin is an important link between inflammation induced by obesity and insulin resistance.

Having demonstrated similarities between mouse resistin and human resistin, Dr. Lazar plans to continue to elucidate the role of resistin in humans and its relationship with obesity, inflammation, and insulin resistance. He noted that the mice that harbor the human version of resistin could provide a model for testing potential therapies to block the actions of human resistin that lead to glucose intolerance and insulin resistance. In addition, scientists in Dr. Lazar's laboratory have created a mouse model that mimics the expression of human resistin even more closely. While in the first mouse model the macrophages continually produce human resistin, in the new mouse model human resistin production is responsive to inflammatory stimuli and is not continually produced. Future studies will include efforts to understand the role of human resistin in obesity and diabetes; cardiovascular disease, including atherosclerosis and heart failure; and inflammatory diseases, such as arthritis. Dr. Lazar hopes to determine whether resistin is a biomarker of and/or a potential risk factor for these conditions. Research from Dr. Lazar and his colleagues has provided great insight into the molecular links between inflammation, obesity, and metabolic diseases. This knowledge could promote the development of therapies to ameliorate the harmful effects of obesity, including insulin resistance and type 2 diabetes.

PATIENT PROFILE

The Gould Family

Dedicated to Participating in Research To Be Part of a Cure for Type 1 Diabetes

The Gould family. Back row, left to right: Sam, Patrick, Ellen, Dave, Andrew, and Nicholas. Front row, left to right: Maggie, Annie, Sarah, and Oliver.
Photo credit: Amy McIntyre

Dave and Ellen Gould of Nashville, Tennessee, have eight children ranging in age from 2 to 17. Within the last 5 years, four of their children have been diagnosed with type 1 diabetes. Even though their lives are busier than most people can imagine, the Goulds make time not only to participate in clinical research studies, but also to tell others about the importance of research toward combating type 1 diabetes and finding a cure.

Their passion and dedication was evident this past summer, when Ellen testified in Congress at a hearing held in conjunction with the Juvenile Diabetes Research Foundation's 2009 Children's Congress. In her testimony, Ellen related how, on a Saturday morning several months earlier, the family was awakened by then 12-year-old son, Sam, who had collapsed in his room, incoherent, because of a dangerously low blood sugar level. "It took us 20 minutes to get him back to normal," Ellen said. "But what happens the next time if we don't hear him? As their mother, I just want to reach out and make it better—but I can't. I can't cure this disease; I can't make it better for my kids. I need help. Finding a cure means everything to my family, and we are willing to be part of the solution."

"Finding a cure means everything to my family, and we are willing to be part of the solution," said Ellen.

To that end, the Goulds are participating in NIDDK's Type 1 Diabetes TrialNet, an international network of researchers exploring new strategies to prevent, delay, and reverse type 1 diabetes. TrialNet is also supported by the *Special Statutory Funding Program for Type 1 Diabetes Research*.

"There are a lot of smart people working on a cure for this disease," Dave said in a later interview. "I'm an optimist. I believe a cure is coming, and if my family can help speed it up a bit by being part of an important study, all the better."

"Diabetes Is Part of Our Family"

Type 1 diabetes is a chronic disease in which the body's immune system launches a misguided attack and destroys the insulin-producing cells of the pancreas. People with the disease need daily administration of insulin, either by injection or with a pump, and must monitor their blood sugar levels vigilantly.

"Diabetes is part of our family," Ellen said. "We're constantly filling prescriptions, scheduling doctors' appointments, filling out forms for school and various activities, educating others—and making sure our kids are safe," she added.

For the Goulds, a life dominated by type 1 diabetes started 5 years ago when their oldest son, Patrick, then 12 years old, was diagnosed with the disease.

"I was watching him lose weight, and as a mother, I knew something was wrong," Ellen said. "I even asked Dave, 'do you think it could be diabetes?'"

As fate would have it, the family was on vacation when Ellen came upon a 1974 edition of *Life Magazine* at a flea market. The cover story just happened to be "Does Your Child Have Diabetes?" It was all the impetus she needed. As soon as the vacation ended, Ellen brought Patrick to their pediatrician and a blood test revealed that he had the disease. "Patrick's diagnosis came as a complete shock," Ellen said. "There's no history of diabetes in Dave's or my families."

Eighteen months later, their daughter Sarah, then 6 years old, began losing weight and urinating frequently at night. She too was diagnosed with type 1 diabetes. "Sarah took it very cavalierly, just like a trooper," says Ellen. But when Ellen and Dave told Patrick of his sister's diagnosis, "he just broke down and cried. Since having been diagnosed, Patrick had always dealt with his diabetes well and never really complained. But at that moment we knew how bad it was for him," said Ellen.

Shortly after Sarah was diagnosed, the family's endocrinologist told them about TrialNet, in which researchers were looking for children whose siblings had type 1 diabetes to see if other children in the family were at risk for developing the disease.

Dave said that at first he and Ellen didn't want to have their other children screened for the disease. "We just didn't want that cloud hanging over our heads," Ellen added. However, the more they thought about it, the more they began to realize that "maybe we can learn something from this. We also felt strongly that we needed to be part of this search for a cure, and the more we thought about it, the more enthusiastic we became," said Dave. It was through a TrialNet screening that the Goulds learned that then 10-year-old Sam also had type 1 diabetes.

Participating in a Clinical Trial To Prevent Type 1 Diabetes

A clinical trial being conducted by TrialNet is building on the results of a previous NIDDK-supported clinical trial, called the Diabetes Prevention Trial-Type 1 (DPT-1). The DPT-1 studied whether injected or oral insulin administration could prevent or delay type 1 diabetes in persons at high or moderate risk for the disease. While the DPT-1 did not find an overall protective effect of injected or oral insulin, a subset of trial participants who had higher levels of a predictive marker of the disease (insulin autoantibodies) seemed to benefit from oral insulin treatment, though this result was not definitive. TrialNet is now building on these observations, and has launched a clinical trial to determine if oral insulin therapy could prevent the disease in people with elevated insulin autoantibodies.

Through a TrialNet screening, the Goulds learned that 4-year-old Oliver had elevated levels of insulin autoantibodies, which made him eligible to enroll in the TrialNet oral insulin prevention study. The Goulds enrolled Oliver in the study, which randomly assigns participants to receive either an insulin pill or a placebo (inactive pill without insulin). Those participating in the trial do not know whether they are getting the insulin or the placebo. This randomization allows researchers to compare the two groups to determine if oral insulin could prevent or delay the development of type 1 diabetes.

Oliver has since developed type 1 diabetes—the fourth of the Gould's children to be diagnosed with the disease—and, until the study is over, the family will not know whether he received insulin or placebo. "When we decided to enroll Oliver in the study,

PATIENT PROFILE

friends would ask, 'if you don't know whether he's receiving insulin or placebo, why did you enroll him?'" said Dave. "Ellen's and my response to them is: that's what research is. You have to be willing to accept that when you get into a study like this." He quickly added that, "We would be ready, willing, and able to do it all again. The best thing about TrialNet is that it's helping all of us move closer to preventing or delaying type 1 diabetes."

Likewise, significant knowledge will be gained no matter the outcome of the trial—it is only through a rigorous clinical trial that researchers definitively learn which therapies work and which ones don't. When effective therapies or preventative approaches are found, other patients and people at risk can benefit from them. If a potential intervention turns out to be ineffective, then scientists know to explore other avenues to find therapies that work. It is thanks to the dedication of the Goulds and other families that this important new knowledge can be gained.

"When we decided to enroll Oliver in the TrialNet study, friends would ask, 'if you don't know whether he's receiving insulin or placebo, why did you enroll him?'" said Dave. "Ellen's and my response to that is: that's what research is. You have to be willing to accept that when you get into a study like this." He quickly added that, "We would be ready, willing, and able to do it all again."

Fortunately, the Gould's other four children—Maggie, Annie, Nicholas, and Andrew—so far have tested negative for early markers of type 1 diabetes. But that doesn't mean that they are not affected by the disease. According to Ellen, 3-year-old Annie asks "When I am I going to get diabetes?" and 2-year-old Maggie tries putting Patrick's glucose meter on her finger to test herself. Describing his perspective on this disease, 13-year-old Nicholas said, "I'm really glad I don't have it. I see what my brothers and sister have to go through every day. I try to help as best I can, but I'm worried about them."

But Dave lays claim to being the family's ultimate worry-wart. "Ever since Sam's low blood sugar episode, I'm up with every bump I hear during the night, checking their bedrooms."

Through another study being conducted by TrialNet—the Natural History Study—the Gould's four children who don't have type 1 diabetes will continue to be screened annually. For the four who do have the disease, the best news to date is that they are all doing well and show no signs of complications from the disease.

"When I was first diagnosed," Patrick said, "I got a note from someone in the Juvenile Diabetes Research Foundation, and it said 'Hang in there. There's a cure coming. Take as good care of yourself as you can; you're not going to have to do this much longer.' My message to others with type 1 diabetes is the same: There's a cure coming. Hang in there."

As for his mother's testifying in front of Congress with her urgent message for finding a cure for her children and all the others who must deal with type 1 diabetes every minute of every day, Patrick said: "She was awesome!"

For information about participating in Type 1 Diabetes TrialNet, please call 1-800-HALT-DM1 or visit *www.diabetestrialnet.org*

PATIENT PROFILE

Leon Gibbs

Participant in Diabetes Prevention Program Outcomes Study (DPPOS) Continues To Be Diabetes-Free

Leon Gibbs

About 12 years ago, a doctor friend noticed that Leon Gibbs, then in his late 50s, was putting on weight. Knowing that diabetes runs in Leon's family, the friend urged, "Why don't you sign up for a study I'm involved in, called the Diabetes Prevention Program (DPP)?"

Leon took his physician friend's advice, and as a result became one of 3,234 people selected from around the country to determine if a modest amount of weight loss due to diet and exercise can prevent or delay the onset of type 2 diabetes. The study also tested whether a diabetes drug, metformin, could prevent onset of the disease. Participants were selected from a variety of ethnic backgrounds and cultures. All were either overweight or obese adults, and all had elevated blood glucose levels, making them high-risk candidates for type 2 diabetes.

Leon admits that the program was a challenge for him. "I'm not the best exercise person," Leon says, and healthy foods, like salads, had never been a part of his daily diet. But he persevered. He lost weight and gained weight, but remained diabetes-free throughout the duration of the original study. He was so impressed with the program that when a follow-up study was offered, called the Diabetes Prevention Program Outcomes Study (DPPOS), he signed up without hesitation.

"I owe a lot of thanks to the original prevention program, as well as to the follow-up outcomes study," says Leon, who now, at age 69, remains diabetes-free, healthy and active. "Just recently a friend complimented me on how good I look," says Leon. "I told him about the program and how much better I feel as a result of taking part in it."

"I owe a lot of thanks to the original prevention program, as well as to the follow-up outcomes study," says Leon, who now, at age 69, remains diabetes-free, healthy and active. "Just recently a friend complimented me on how good I look," says Leon. "I told him about the program and how much better I feel as a result of taking part in it."

Building Knowledge on Past Research

The studies Leon participated in—the DPP and the ongoing DPPOS—have taken researchers a long way in establishing that lifestyle intervention, such as diet and exercise, can reduce the risk of type 2 diabetes. In fact, the results of the original DPP study, which began in 1998, were so overwhelmingly positive they were announced a year earlier than scheduled.

The DPP study demonstrated that both lifestyle changes and metformin are effective at reducing the risk of diabetes—the lifestyle changes especially so. After 3 years, those who participated in the lifestyle intervention portion of the study reduced their risk for development of type 2 diabetes by 58 percent, and study participants who took metformin reduced their risk by 31 percent, compared with placebo.

Getting with the Program

When he entered the DPP study, however, Leon was none too happy when he learned that he had been selected for the lifestyle intervention group. "I really did not want to diet and exercise. I wanted to take the easy way out and do the pill," he now chuckles. But knowing that his mother's two sisters had type 2 diabetes (one of whom subsequently died from the disease), he decided that joining the study was a good idea.

As part of the DPP, Leon started walking in his neighborhood and, using a pedometer, began keeping track of how many steps he took in a day, as well as his daily caloric intake. The program offered cooking classes and classes on how to read labels when shopping for food. "It's been a good lesson," Leon says of the program. He adds that he now stays away from sodium and sodas, eats less meat and more salads, and says he feels a lot better for it. As Leon began feeling more confidence in the program and in himself, he says, "I gradually got the gumption to ask waiters when I eat out, 'what's the most heart-healthy thing on your menu?'"

But controlling his weight hasn't exactly been a straight-line process for Leon. After retiring in 1991 weighing 200 pounds, he and his wife of 45 years, Doris, purchased a retail franchise and worked the evening shift together. After closing the place at 9 p.m., they would go home and eat late, and according to Leon, not-so-healthy dinners. As far as his diet and exercise during that period, Leon admits "I went through a lot of failure between 1991 and 1997." He entered the DPP 31 pounds heavier than he had been at "retirement." Even during the studies, his weight has continued to fluctuate.

Life-long Lessons

Leon jokes with family and friends that ever since he was in the DPP, and now the DPPOS follow-up study, he's probably lost 1,000 pounds—"and luckily I've only regained 995 of it back," he laughs. It makes for a good line, but there is clearly more to Leon's story. Despite the fact that Leon says he has gone through several periods of extreme enthusiasm followed by setbacks after he loses weight, the lessons he has learned from both of these studies obviously have stuck with him.

Two years ago, Leon bought a bike and began using it. He also walks 3 to 5 days a week and in the past year, his weight has gone from 242 pounds down to 214 pounds. To keep himself motivated and active, and being an avid golfer, he recently bought himself a new set of clubs. "My waistline has gone from 46 to 42 inches; I can do more now that I feel lighter," says the 6-foot-tall Leon. "And my wife and I have since sold our franchise, and as a result, I don't eat anything after 5 p.m. anymore," he says.

Leon continues to stay active in the DPPOS study. At visits he provides blood and urine samples, is administered an electrocardiogram to test his heart function, has his weight and height tracked and is asked if there have been any changes in his life since he was last seen. "Now they're also asking things that relate to your mental state, things like 'Are you more or less happy with your life?'" Leon says.

Study program staff also discovered that Leon had high blood pressure, as well as some high cholesterol levels. He appreciates that the study staff always send his medical records to his primary care physician and other doctors that he sees. "It's a very effective and efficient operation and takes a lot of redundancy out of my health care," he adds.

"From time to time the study folks send us literature on how to stay healthy," says Leon. But the thing he likes best are the booster classes, where he gets to share his experiences with others who are going through the same experience of having to diet and lose weight to stay healthy.

"I've learned a great deal about how to modify my eating habits, but it's hard to keep the weight off at my age," Leon adds, "that's why I like talking to people who are struggling with the same issues that I'm struggling with."

Leon has become a strong advocate of DPP and DPPOS, to the point where he has brought his wife to some of the classes the study offers on eating healthily. He even promotes healthy lifestyle changes to his 42-year-old son and his wife. "Unfortunately," he says, "they don't take my advice too seriously, but maybe one day they'll remember what I've told them."

Knowing how hard it is to lose weight, Leon says "You've got to change your mental attitude and be more mindful of what you put in your body. You've got to do everything you can to stay active. Keep moving. The rewards are worth it."

"You've got to change your mental attitude and be more mindful of what you put in your body. You've got to do everything you can to stay active. Keep moving. The rewards are worth it."

Though his blood glucose numbers "are still on the watch list, I remain diabetes-free," Leon says proudly.